

## Radiation Field Design in the ACOSOG Z0011 (Alliance) Trial

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See accompanying editorial on page 3583; listen to the podcast by Dr Wright at [www.jco.org/podcasts](http://www.jco.org/podcasts)

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Published online ahead of print at [www.jco.org](http://www.jco.org) on August 18, 2014.



Processed as a Rapid Communication manuscript.

Written on behalf of the Alliance for Clinical Trials in Oncology.

Supported by National Cancer Institute (NCI) Grant No. U10 CA 76001 to the American College of Surgeons Oncology Group and in part by NCI Grants No. CA31946 to the Alliance for Clinical Trials in Oncology and No. CA33601 to the Alliance Statistics and Data Center.

Terms in blue are defined in the glossary, found at the end of this article and online at [www.jco.org](http://www.jco.org).

Authors' disclosures of potential conflicts of interest are found in the article online at [www.jco.org](http://www.jco.org). Author contributions are found at the end of this article.

Clinical trial information: NCT00003855.

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0732-183X/14/3232w-3600w/\$20.00

DOI: 10.1200/JCO.2014.56.5838

### ABSTRACT

#### Purpose

ACOSOG Z0011 established that axillary lymph node dissection (ALND) is unnecessary in patients with breast cancer with one to two positive sentinel lymph nodes (SLNs) who undergo lumpectomy, radiotherapy (RT), and systemic therapy. We sought to ascertain RT coverage of the regional nodes in that trial.

#### Methods

We evaluated case report forms completed 18 months after enrollment. From 2012 to 2013, we collected all available detailed RT records for central review.

#### Results

Among 605 patients with completed case report forms, 89% received whole-breast RT. Of these, 89 (15%) were recorded as also receiving treatment to the supraclavicular region. Detailed RT records were obtained for 228 patients, of whom 185 (81.1%) received tangent-only treatment. Among 142 with sufficient records to evaluate tangent height, high tangents (cranial tangent border  $\leq 2$  cm from humeral head) were used in 50% of patients (33 of 66) randomly assigned to ALND and 52.6% (40 of 76) randomly assigned to SLND. Of the 228 patients with records reviewed, 43 (18.9%) received directed regional nodal RT using  $\geq$  three fields: 22 in the ALND arm and 21 in the SLND arm. Those receiving directed nodal RT had greater nodal involvement ( $P < .001$ ) than those who did not. Overall, there was no significant difference between treatment arms in the use of protocol-prohibited nodal fields.

#### Conclusion

Most patients treated in Z0011 received tangential RT alone, and some received no RT at all. Some patients received directed nodal irradiation via a third field. Further research is necessary to determine the optimal RT approach in patients with low-volume axillary disease treated with SLND alone.

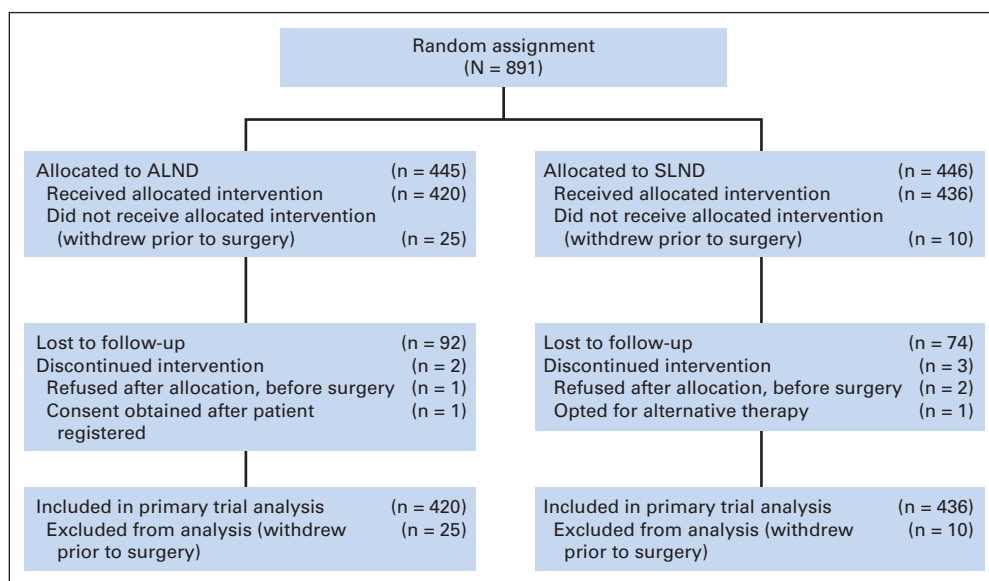
*J Clin Oncol* 32:3600-3606. © 2014 by American Society of Clinical Oncology

### INTRODUCTION

The ACOSOG (American College of Surgeons Oncology Group) Z0011 trial randomly assigned patients with clinically node-negative T1 or T2 breast cancer with one or two positive **sentinel lymph nodes** (SLNs), for whom breast-conserving therapy was planned, to completion axillary lymph node dissection (ALND) versus no ALND.<sup>1,2</sup> At a median follow-up of 6.3 years, there were no differences in overall survival or locoregional recurrence between patients receiving ALND or SLND alone. This practice-changing trial<sup>3-5</sup> established that ALND is unnecessary after SLN biopsy in patients with breast cancer like those enrolled who receive lumpec-

tomy, whole-breast radiation therapy (RT), and systemic therapy.

Although the Z0011 protocol required that patients receive whole-breast RT using standard tangential fields and specified that a third field of directed nodal treatment should not be used, the extent of RT coverage of the regional nodes in these patients has not previously been described; however, it has been the subject of considerable speculation.<sup>6-8</sup> It has been hypothesized that radiation oncologists, who could not be blinded to patients' treatment assignments and who had discretion over the extent of the axillary contents included in tangential fields, might have systematically treated patients on the SLN-only arm with high tangents to include a component of axillary level I/II more often than those in



**Fig 1.** CONSORT diagram. ALND, axillary lymph node dissection; SLND, sentinel lymph node dissection.

the ALND arm.<sup>9</sup> The goal of this study was to review the RT treatment records to determine if there were differences in RT delivery based on extent of axillary surgery.

## METHODS

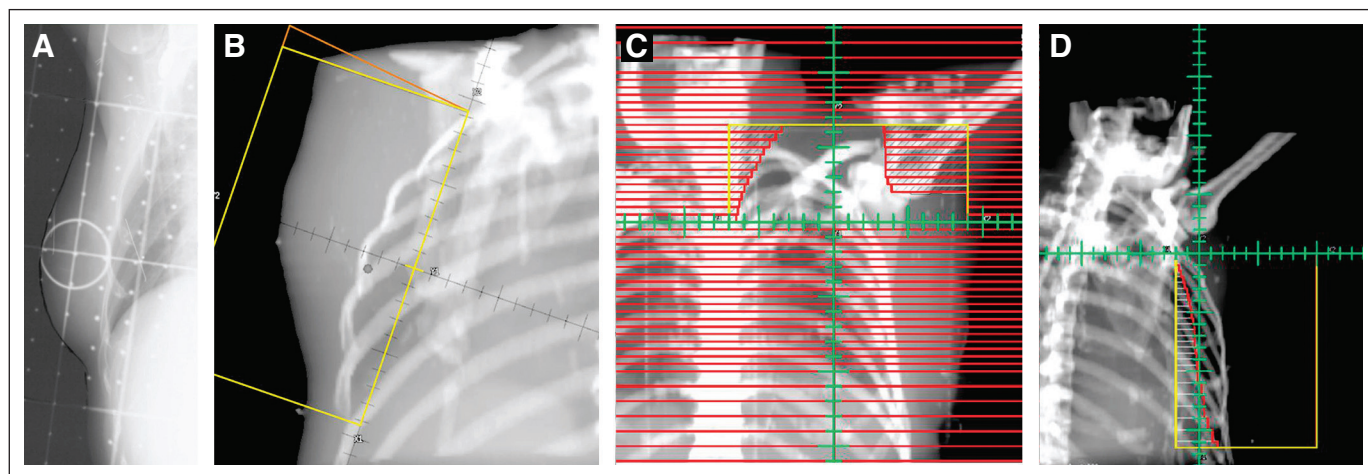
After approval by local independent review boards, ACOSOG Z0011 enrolled patients after informed consent between May 1999 and December 2004, with a total of 891 patients randomly assigned (Fig 1). Of these, 35 patients withdrew consent from the study and were excluded from all analyses of the trial. The remaining 856 patients constituted the intent-to-treat sample that has been previously analyzed for reporting of outcomes (Fig 1).

Information on RT administered to patients enrolled onto Z0011 was collected in case report forms completed by enrolling providers approximately 18 months after enrollment. With respect to radiation field information, the response options on the case report forms included breast, supraclavicular, and other.

Between January 2012 and June 2013, investigators were contacted to identify all treating radiation oncology practices to request more detailed radiation treatment records for central review, as was allowed by the trial protocol. Treating radiation oncologists as well as radiation oncologists currently practicing at these facilities were contacted to request detailed radiation records for each patient.

Radiation treatment data were sent to the Quality Assurance Review Center,<sup>10</sup> and the deidentified information was reviewed by two independent radiation oncologists, who were blinded regarding the arm to which patients were randomly assigned. These radiation oncologists evaluated whether a third field had been used, as well as the distance from the cranial border of the tangential field to the humeral head. As previously described by Schlembach et al,<sup>11</sup> we considered those in whom the cranial border of the medial tangential field was within 2 cm of the humeral head to have received high tangents. Examples of different field arrangements in the records we received are depicted in Figure 2.

We determined the distribution of responses regarding administration of a third field, both within the larger sample of patients for whom case report



**Fig 2.** Representative examples of detailed radiation treatment records received and classified as receiving standard tangents, high tangents, or third-field treatment. (A) Standard tangents. (B) High tangents. (C and D) Third-field and matched tangents from a single patient.

forms were available and within the subset of patients for whom we were able to conduct detailed review of radiation records. We evaluated the characteristics of those patients for whom we received radiation records and compared them with those known to have received RT according to the case report forms but for whom detailed records were not obtained. Finally, we evaluated the

correlates of receipt of a third field, as well as receipt of high tangents versus standard tangents, within this group.

The analyses were performed using data available as of June 7, 2013. Continuous data between groups were compared with a two-sample *t* test. Fisher's exact test was used to compare categorical variables. Univariable and multivariable logistic regression were used to identify patient and tumor characteristics associated with treatment by high tangents. Analyses were performed with SAS software (version 9.3; SAS Institute, Cary, NC). All tests were two sided, and *P* values less than .05 were considered statistically significant. ACOSOG is now part of the Alliance for Clinical Trials in Oncology (Alliance), and statistical analyses were performed by Alliance statisticians.

**Table 1.** Comparison of Respondents Versus Nonrespondents to Request for Detailed RT Records

Characteristic	Total (n = 589)		RT Details Obtained by QARC (n = 228)		RT Details Not Obtained by QARC (n = 361)		<i>P</i>
	No.	%	No.	%	No.	%	
Study arm							.23
ALND	288	48.9	104	45.6	184	51.0	
SLND	301	51.1	124	54.4	177	49.0	
Age, years							.17
Mean		56.1		55.5		56.6	
SD		11.7		10.9		12.1	
Median		55.0		54.0		56.0	
Range		24.0-90.0		32.0-90.0		24.0-85.0	
Missing		8		3		5	
Clinical T stage							.64
T1	408	69.9	162	71.1	246	69.1	
T2	176	30.1	66	28.9	110	30.9	
Missing	5		0		5		
Clinical tumor size, cm							.60
Mean		1.8		1.8		1.8	
SD		0.8		0.8		0.9	
Median		1.7		1.6		1.7	
Range		0.1-6.0		0.4-4.0		0.1-6.0	
Missing		15		1		15	
Receptor status							.28
ER positive/PR positive	367	67.2	143	68.4	224	66.5	
ER positive/PR negative	79	14.5	27	12.9	52	15.4	
ER negative/PR positive	7	1.3	5	2.4	2	0.6	
ER negative/PR negative	93	17.0	34	16.3	59	17.5	
Missing	43		19		24		
LVI status							1.00
Yes	167	37.5	68	37.4	99	37.6	
No	278	62.5	114	62.6	164	62.4	
Missing	144		46		98		
Modified Bloom-Richardson score							.20
1	105	24.1	40	23.5	65	24.4	
2	212	48.6	91	53.5	121	45.5	
3	119	27.3	39	22.9	80	30.1	
Missing	153		58		95		
Tumor type							.20
Ductal	487	83.8	184	82.1	303	84.9	
Lobular	44	7.6	15	6.7	29	8.1	
Other	50	8.6	25	11.2	25	7.0	
Missing	8		4		4		
No. of lymph node metastases							.60
0-1	375	69.8	143	67.4	232	71.4	
2	102	19.0	44	20.8	58	17.8	
≥ 3	60	11.7	25	11.8	35	10.8	
Missing	52		16		36		

NOTE. From among patients known to have been treated with RT.  
Abbreviations: ALND, axillary lymph node dissection; ER, estrogen receptor; LVI, lymphovascular invasion; PR, progesterone receptor; QARC, Quality Assurance Review Center; RT, radiation therapy; SD, standard deviation; SLND, sentinel lymph node dissection.

**Table 2.** Comparison Between Arms for Patients Treated With RT for Whom Detailed Records Were Available

Characteristic	Total (n = 228)		ALND Arm (n = 104)		SLND Arm (n = 124)		<i>P</i>
	No.	%	No.	%	No.	%	
Age, years							.34
Mean		55.5		56.1		54.9	
SD		10.9		11.2		10.6	
Median		54.0		55.0		53.0	
Range		32.0-90.0		32.0-80.0		33.0-90.0	
Missing		3		2		1	
Clinical T stage							.46
T1	162	71.1	71	68.3	91	73.4	
T2	66	28.9	33	31.7	33	26.6	
Missing	0		0		0		
Clinical tumor size, cm							.55
Mean		1.8		1.8		1.7	
SD		0.8		0.7		0.8	
Median		1.6		1.6		1.6	
Range		0.4-4.0		0.4-4.0		0.6-4.0	
Missing		1		0		1	
Receptor status							.51
ER positive/PR positive	143	68.4	69	71.9	74	65.5	
ER positive/PR negative	27	12.9	13	13.5	14	12.4	
ER negative/PR positive	5	2.4	1	1.0	4	3.5	
ER negative/PR negative	34	16.3	13	13.5	21	18.6	
Missing	19		8		11		
LVI status							.17
Yes	68	37.4	36	42.9	32	32.7	
No	114	62.6	48	57.1	66	67.3	
Missing	46		20		26		
Modified Bloom-Richardson score							.36
1	40	23.5	16	20.3	24	26.4	
2	91	53.5	47	59.5	44	48.4	
3	39	22.9	16	20.3	23	25.3	
Missing	58		25		33		
Tumor type							.047
Ductal	184	82.1	78	76.5	106	86.9	
Lobular	15	6.7	7	6.9	8	6.6	
Other	25	11.2	17	16.7	8	6.6	
Missing	4		2		2		
No. of lymph node metastases							< .001
0-1	143	67.5	55	58.5	88	74.6	
2	44	20.8	19	20.2	25	21.2	
≥ 3	25	11.8	20	21.3	5	4.2	
Missing	16		10		6		

Abbreviations: ALND, axillary lymph node dissection; ER, estrogen receptor; LVI, lymphovascular invasion; PR, progesterone receptor; RT, radiation therapy; SD, standard deviation; SLND, sentinel lymph node dissection.

## RESULTS

Of the 856 patients who were analyzed in the primary report on trial outcomes, case report forms regarding RT administration were available for 605 patients. As previously reported,<sup>2</sup> 540 of these patients (89%) were noted to have received whole-breast RT. Of these, 89 patients (15% of 605) were recorded as also receiving treatment to the supraclavicular region.

We attempted to obtain detailed radiation records for 791 patients (540 patients known to have received RT plus 251 for whom adjuvant RT case report forms were not completed). Detailed RT records were received for central review for 228 of these patients (29%). Of these, 104 were from the ALND arm (26.7% of 389 patients randomly assigned to this arm), and 124 were from the SLND arm (30.7% of 404 patients randomly assigned to this arm). Among the 228 patients for whom detailed RT records were available, 138 had documentation of three-dimensional treatment planning.

Comparison between patients with RT information available and those for whom RT was known to have been administered but detailed records were not submitted is summarized in Table 1. Patients with RT information available did not differ significantly from those for whom it was not.

Clinical characteristics of the 228 patients for whom detailed RT records were available are listed in Table 2. Within this subgroup of trial patients, patients in the SLND arm were more likely to have ductal tumors (86.9%) than patients in the ALND arm (76.5%;  $P = .047$ ). In addition, as in the overall sample previously analyzed, patients in the SLND arm had fewer lymph node metastases ( $P < .001$ ).

Of the 228 patients with detailed RT records evaluated, 185 patients (81.1%) received tangent-only treatment (Fig 3). Among these 185 patients, there were sufficient data to evaluate tangential field height in 142 (76.8%). High-tangent RT fields were used in 50% of patients (33 of 66) randomly assigned to the ALND arm and 52.6% of patients (40 of 76) randomly assigned to the SLND arm. Table 3 summarizes the association between treatment arm and various patient characteristics with use of a high-tangent field within the subgroup with evaluable tangents. Of note, treatment arm was not associated with use of high-tangent RT on either univariable or multivariable analysis.

Of the 228 patients with records reviewed, 43 (18.9%) received directed regional nodal RT using  $\geq$  three fields: 22 in the ALND arm

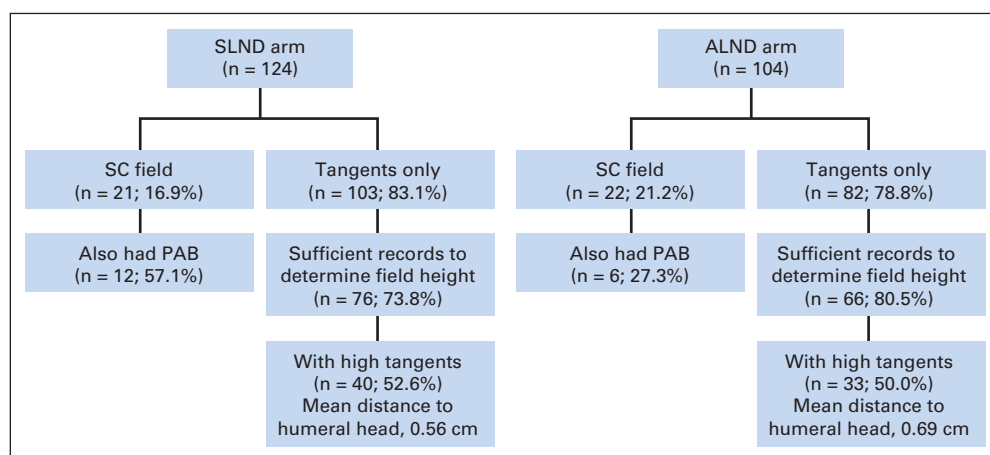
and 21 in the SLND arm. Within the small group receiving a third field, treatment of a posterior axillary boost field was more common in patients who received SLN biopsy alone, but this difference did not achieve statistical significance (12 of 21 v six of 22;  $P = .067$ ).

We used multivariable models to evaluate patient characteristics associated with use of a third field, with treatment arm as an adjusting variable (Table 4). Those receiving nodal RT had a greater number of lymph nodes involved ( $P < .001$ ) than those who did not. Of the three patients with zero nodes involved (all of whom were in SLND arm), one received directed nodal RT (using at least one third supraclavicular field). Of the 140 patients with one node involved, 13 (9.3%) received directed nodal RT: four (7.3%) of the 55 patients with one node involved in the ALND arm and nine (10.6%) of the 85 patients with one node involved in the SLND arm. Of the 44 patients with two nodes involved, nine (20.5%) received directed nodal RT: three (15.8%) of the 19 patients with two nodes involved in the ALND arm and six (24.0%) of the 25 patients with two nodes involved in the SLND arm. Of the nine patients with three nodes involved, five (55.6%) received directed nodal RT: two (33.3%) of the six patients with three nodes involved in the ALND arm and three (100.0%) of the three patients with three nodes involved in the SLND arm. Of the 16 patients with  $\geq$  four nodes involved, 13 (81.3%) received directed nodal RT: 11 (78.6%) of the 14 patients with  $\geq$  four nodes involved in the ALND arm and two (100.0%) of the two patients with  $\geq$  four nodes involved in the SLND arm. There was no significant difference between the two arms in the use of protocol-prohibited nodal RT fields.

## DISCUSSION

In this analysis of radiation fields administered to patients in the Z0011 trial, we found that most patients received tangential field RT alone, and we observed no significant differences in tangential field height between the two study arms. However, we observed that a nontrivial percentage of patients in both arms received directed nodal irradiation via a third field, contrary to protocol requirements. In the subgroup of patients for whom detailed RT records were available, the highest rates of directed nodal irradiation were among those with multiple nodes involved.

The optimal management of regional lymph nodes in early-stage breast cancer has long been the subject of investigation. Four decades



**Fig 3.** Distribution of patients for whom detailed radiation treatment records were available. ALND, axillary lymph node dissection; PAB, posterior axillary boost; SC, supraclavicular; SLND, sentinel lymph node dissection.



**Table 3.** Comparison Between Patients Treated With High Versus Standard Tangents

Characteristic	Total (n = 142)		Standard Tangents (n = 69)		High Tangents (n = 73)		P
	No.	%	No.	%	No.	%	
Study arm							.87
ALND	66	46.5	33	47.8	33	45.2	
SLND	76	53.5	36	52.2	40	54.8	
Age, years							.84
Mean		55.6		55.6		55.5	
SD		10.7		11.3		10.1	
Median		54.0		53.0		56.0	
Range		36.0-79.0		36.0-79.0		38.0-79.0	
Missing		3		1		2	
Clinical T stage							.10
T1	97	68.3	52	75.4	45	61.6	
T2	45	31.7	17	24.6	28	38.4	
Missing	0		0		0		
Clinical tumor size, cm							.046
Mean		1.8		1.6		1.9	
SD		0.8		0.8		0.8	
Median		1.7		1.5		2.0	
Range		0.4-4.0		0.4-4.0		0.6-4.0	
Missing		1		0		1	
Receptor status							.69
ER positive/PR positive	91	69.5	40	64.5	51	73.9	
ER positive/PR negative	15	11.5	8	12.9	7	10.1	
ER negative/PR positive	3	2.3	2	3.2	1	1.4	
ER negative/PR negative	22	16.8	12	19.4	10	14.5	
Missing	11		7		4		
LVI status							.85
Yes	41	35.0	19	33.3	22	36.7	
No	76	65.0	38	66.7	38	63.3	
Missing	25		12		13		
Modified Bloom-Richardson score							.11
1	28	25.9	17	34.0	11	19.0	
2	62	57.4	28	56.0	34	58.6	
3	18	16.7	5	10.0	13	22.4	
Missing	34		19		15		
Tumor type							.15
Ductal	108	77.1	57	83.8	51	70.8	
Lobular	12	8.6	5	7.4	7	9.7	
Other	20	14.3	6	8.8	14	19.4	
Missing	2		1		1		
No. of lymph node metastases							.59
0-1	97	74.0	50	78.2	47	70.2	
2	29	22.1	12	18.8	17	25.4	
≥ 3	5	3.8	2	3.1	3	4.5	
Missing	11		5		6		

NOTE. From among those with evaluable tangential fields.

Abbreviations: ALND, axillary lymph node dissection; ER, estrogen receptor; LVI, lymphovascular invasion; PR, progesterone receptor; SD, standard deviation; SLND, sentinel lymph node dissection.

**Table 4.** Logistic Models for Treatment With Supraclavicular RT for Patients Treated With RT for Whom Detailed Records Available

Variable	OR	95% CI	P
Age, years	0.99	0.96 to 1.02	.41
Arm	1.36	0.70 to 2.65	.37
Clinical T stage (T1 v T2)	1.08	0.52 to 2.27	.83
Arm	1.32	0.68 to 2.57	.41
Clinical tumor size	1.05	0.68 to 1.62	.84
Arm	1.30	0.67 to 2.53	.44
Hormone receptor status (positive v negative)	1.18	0.42 to 3.33	.75
Arm	1.82	0.88 to 3.76	.11
LVI (present v absent)	0.74	0.33 to 1.68	.48
Arm	2.10	0.92 to 4.76	.073
Modified Bloom-Richardson score			.74
1	0.68	0.21 to 2.22	
2	0.70	0.27 to 1.85	
3	1.00	Reference	
Arm	2.19	0.96 to 5.02	.063
Tumor type			.073
Ductal	7.46	0.97 to 57.54	
Lobular	1.92	0.11 to 33.34	
Other	1.00	Reference	
Arm	1.72	0.86 to 3.43	.13
No. of lymph node metastases			< .001
0-1	1.00	Reference	
2	2.48	0.98 to 6.25	
≥ 3	34.12	10.54 to 110.42	
Arm	0.49	0.20 to 1.22	.12

NOTE. Models adjusted for arm assignment: ALND versus SLND.

Abbreviations: ALND, axillary lymph node dissection; LVI, lymphovascular invasion; OR, odds ratio; RT, radiation therapy; SLND, sentinel lymph node dissection.

who underwent total mastectomy alone experienced axillary recurrence as a first event,<sup>13</sup> suggesting the possibility that it may not be necessary to provide directed locoregional treatment to all axillary nodal disease.

The ACOSOG Z0011 trial built on this work by seeking to determine whether axillary node dissection could be safely omitted in patients with clinically negative axillae who had one to two nodes found to be positive on sentinel node biopsy, in the setting of breast conservation with adjuvant whole-breast RT and modern systemic therapy. Outcomes in Z0011 have been previously reported to be equivalent, and axillary recurrences were reassuringly rare (0.9%) among the patients who did not receive axillary dissection.<sup>1</sup> Indeed, the observation of such low regional failure rates despite the 27% incidence of additional nodal disease among patients randomly assigned to axillary dissection led the investigators and others to speculate that incidental irradiation of the low axilla with standard tangential fields may have played an important role in ensuring the excellent outcomes observed in Z0011.<sup>1,14</sup> This, in turn, motivated our interest in performing our study, which primarily sought to document the extent to which radiation fields incidentally or intentionally covered the axilla in patients treated in Z0011.

Our findings that tangent height did not differ between the two study arms suggest that radiation oncologists did not intentionally alter their tangential fields to cover more of the axilla in patients receiving sentinel node biopsy alone in this trial. Still, it is noteworthy

ago, the NSABP (National Surgical Adjuvant Breast and Bowel Project) B-04 trial randomly assigned clinically node-negative patients to radical mastectomy, total mastectomy with nodal irradiation, or total mastectomy alone (with delayed axillary dissection for those with axillary recurrence). In that study, survival outcomes were equivalent in the three arms. Moreover, although 39% of patients who underwent radical mastectomy were node positive,<sup>12</sup> only 19% of patients

that in approximately half of patients treated in both arms, the superior border of the tangential field was within 2 cm of the humeral head and may have led to substantial incidental axillary irradiation. A previous study has suggested that the average dose delivered to the level I axilla increases from 66% of prescribed dose with standard tangents to 86% with high tangents, and average dose to level II increases from 44% to 71%. The proportion of level I receiving 95% of prescribed dose increases from 51% with standard tangents to 79% with high tangents, and the proportion of level II receiving 95% of prescribed dose increases from 26% to 51%.<sup>15</sup> Therefore, consistent with prior reports from the Z0011 trialists, we believe that the results of Z0011 should not be extrapolated to patients who do not receive adjuvant RT or to those who receive RT using partial-breast or prone techniques, in which substantially less of the axilla is included.

Our finding that a substantial minority of patients received extended nodal irradiation, including at least the supraclavicular and infraclavicular (axillary level III) lymph nodes, was unexpected. Controversy persists regarding the optimal radiation field design for the treatment of breast cancer. The preliminary results of the NCIC (National Cancer Institute of Canada) MA20<sup>16</sup> and EORTC (European Organisation for Research and Treatment of Cancer) 22922<sup>17</sup> studies have suggested that irradiation of the supraclavicular and internal mammary nodal regions may affect the rate of distant metastases developing in node-positive patients who receive axillary lymph node dissection. Whether such treatment might benefit patients with minimal axillary disease detected on sentinel node biopsy remains unknown; a trial randomly assigning sentinel node–positive patients to breast only or breast plus regional nodal irradiation would be the ideal way to address the impact of such treatment on patient outcomes. It is also possible that certain patients with limited axillary disease might not require any RT at all; a trial examining whether select patients might avoid both axillary dissection and RT would therefore also be worthy of consideration. These remain important subjects for future investigation, because our findings suggest substantial variability in the extent and even the administration of RT in Z0011.

This study has numerous strengths, including access to detailed RT records of patients treated in a landmark randomized trial. It also has limitations. Most noteworthy is the fact that detailed RT records were only available for approximately one third of patients known to have received RT. Given the long time that has elapsed since treatment, retrieval of these records was impeded by factors such as the loss of archived records and inability to reach treating physicians who had moved or died in the intervening time. Still, we find it reassuring that the rate of third-field treatment in the patients for whom detailed RT records were available was similar to that observed in the larger cohort for whom RT forms were submitted soon after treatment administration. In addition, we are reassured that the patients for whom detailed RT records were available did not differ significantly from patients in

the larger sample when compared on a number of clinical and demographic characteristics. Another limitation is that during the era of the trial, three-dimensional treatment planning was not performed for all patients, which constrained our ability to contour and quantify more specifically the extent of each axillary level included in the treatment fields.

Finally, it is critical to recognize that our observations should not be taken to suggest that the nodal radiation administered to patients in Z0011 was necessary or beneficial. Although we found that a nontrivial minority of patients received more extensive RT than prescribed by the protocol, it is important to note that a subgroup received no RT at all. This is noteworthy not because these protocol violations offset each other but rather because these findings together suggest that future studies are needed to determine whether certain patients might safely avoid RT in these circumstances as well as whether others might benefit from more extensive treatment. Thus, the current findings serve to motivate further research in this area, including trials currently under development in the national cooperative group system. They also support the routine collection in future trials of common data elements related to locoregional treatment, as developed by the National Cancer Institute Breast Oncology Locoregional Disease Task Force,<sup>18</sup> as well as the consideration of real-time RT quality assurance to decrease unwanted heterogeneity in adjuvant treatment design in future studies. In the meantime, these findings continue to support the conclusion in the original publications of the Z0011 trial that patients with positive sentinel nodes who do not undergo axillary dissection should receive at least tangential RT; given the findings of our study, it is not unreasonable to also consider additional nodal treatment in selected patients.

#### AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at [www.jco.org](http://www.jco.org).

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#### REFERENCES

- Giuliano AE, McCall L, Beitsch P, et al: Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: The American College of Surgeons Oncology Group Z0011 randomized trial. *Ann Surg* 252:426-433, 2010
- Giuliano AE, Hunt KK, Ballman KV, et al: Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: A randomized clinical trial. *JAMA* 305:569-575, 2011
- Massimino KP, Hessman CJ, Ellis MC, et al: Impact of American College of Surgeons Oncology Group Z0011 and National Surgical Adjuvant Breast and Bowel Project B-32 trial results on surgeon practice in the Pacific Northwest. *Am J Surg* 203:618-622, 2012
- Gainer SM, Hunt KK, Beitsch P, et al: Changing behavior in clinical practice in response to the ACOSOG Z0011 trial: A survey of the American Society of Breast Surgeons. *Ann Surg Oncol* 19:3152-3158, 2012
- Caudle AS, Hunt KK, Tucker SL, et al: American College of Surgeons Oncology Group (ACOSOG) Z0011: Impact on surgeon practice patterns. *Ann Surg Oncol* 19:3144-3151, 2012
- Giuliano AE: Reply to letter: Are the standard tangential breast irradiation fields used in the ACOSOG Z0011 trial really covering the entire axilla? *Ann Surg* 257:e2, 2013

7. Alco G, Dincer M: Are the standard tangential breast irradiation fields used in the ACOSOG Z0011 trial really covering the entire axilla? *Ann Surg* 257:e1, 2013
8. Belkacemi Y, Allab-Pan Q, Bigorie V, et al: The standard tangential fields used for breast irradiation do not allow optimal coverage and dose distribution in axillary levels I-II and the sentinel node area. *Ann Oncol* 24:2023-2028, 2013
9. Haffty BG, Hunt KK, Harris JR, et al: Positive sentinel nodes without axillary dissection: Implications for the radiation oncologist. *J Clin Oncol* 29:4479-4481, 2011
10. Quality Assurance Review Center. <http://www.qarc.org/>
11. Schlembach PJ, Buchholz TA, Ross MI, et al: Relationship of sentinel and axillary level I-II lymph nodes to tangential fields used in breast irradiation. *Int J Radiat Oncol Biol Phys* 51:671-678, 2001
12. Fisher B, Wolmark N, Bauer M, et al: The accuracy of clinical nodal staging and of limited axillary dissection as a determinant of histologic nodal status in carcinoma of the breast. *Surg Gynecol Obstet* 152:765-772, 1981
13. Fisher B, Jeong JH, Anderson S, et al: Twenty-five-year follow-up of a randomized trial comparing radical mastectomy, total mastectomy, and total mastectomy followed by irradiation. *N Engl J Med* 347:567-575, 2002
14. Caudle AS, Hunt KK, Kuerer HM, et al: Multidisciplinary considerations in the implementation of the findings from the American College of Surgeons Oncology Group (ACOSOG) Z0011 study: A practice-changing trial. *Ann Surg Oncol* 18:2407-2412, 2011
15. Reznik J, Cicchetti MG, Degaspe B, et al: Analysis of axillary coverage during tangential radiotherapy to the breast. *Int J Radiat Oncol Biol Phys* 61:163-168, 2005
16. Whelan TJ, Olivetto I, Ackerman I, et al: NCIC-CTG MA.20: An intergroup trial of regional nodal irradiation in early breast cancer. *J Clin Oncol* 29:80s, 2011 (suppl; abstr LBA1003)
17. Poortmans P, Struikmans H, Kirkove C, et al: Irradiation of the internal mammary and medial supraclavicular lymph nodes in stage I to III breast cancer: 10 year results of the EORTC Radiation Oncology and Breast Cancer Groups phase III trial 22922/10925. Presented at the European Cancer Congress, Amsterdam, the Netherlands, September 27-October 1, 2013
18. National Cancer Institute: NCI's progress on IOM goals and recommendations. <http://www.cancer.gov/aboutnci/organization/ccct/steering-committees/breast-cancer>

## GLOSSARY TERMS

**sentinel lymph node:** the lymph node that is anatomically located such that it is the first site of lymph drainage from the location of the primary tumor. It is suspected and assumed that if a malignancy is going to disseminate via the lymphatic system, metastases will first be evident in the sentinel lymph node. In this manner, this lymph node is said to stand guard or sentinel over the metastatic state of the tumor. For many cancers, the sentinel lymph node is biopsied as part of the staging process and presence of macro- or micrometastases in the sentinel lymph node is a negative prognostic factor.

**AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS  
OF INTEREST**

**Radiation Field Design in the ACOSOG Z0011 (Alliance) Trial**

*The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.*

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**Research Funding:** AbbVie

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No relationships to disclose

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No relationships to disclose

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No relationships to disclose

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No relationships to disclose

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No relationships to disclose



### ***Acknowledgment***

We thank Brenda Ginos of Alliance; T.J. FitzGerald, MD; and staff at the Quality Assurance Review Center, especially Kate Schmitter, Joanna Rojcewicz, Karen Morano, and Sandy Kessel, for their efforts to make this project possible. We also thank the numerous physicians, physicists, dosimetrists, therapists, managers, nurses, and research associates who found time in their busy days to locate archived records and submit the requested materials for our study, as well as those who enrolled and cared for patients in the original trial. Finally, we thank the brave patients with breast cancer who participated in this trial.